



## EDITORIAL COMMENT

# Small steps towards the potential of ‘preventive’ treatment of early phosphate loading in chronic kidney disease patients

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## ABSTRACT

Few clinical studies have investigated the value of phosphate (P)-lowering therapies in early chronic kidney disease (CKD) patients in whom hyperphosphataemia has not yet clearly developed and they report conflicting and even unexpected results. In this issue of *Clinical Kidney Journal*, de Krijger *et al.* found that sevelamer carbonate (4.8 g/day for 8 weeks) did not induce a significant reduction of pulse wave velocity (PWV) and that fibroblast growth factor 23 (FGF23) did not decrease despite a decline in 24-h urine P excretion. To some extent these findings challenge the concept that ‘preventive’ P binder therapy to lower FGF23 is a useful approach, at least over this short period of time. Interestingly, in a subgroup of patients with absent or limited abdominal vascular calcification, treatment did result in a statistically significant reduction in adjusted PWV, suggesting that PWV is amenable to improvement in this subset. Interpretation of the scarce and heterogeneous observations described in early CKD remains difficult and causality and/or the possibility of ‘preventive’ treatment may not yet be completely disregarded. Moreover, de Krijger *et al.* contribute to the identification of new sources of bias and methodological issues that may lead to more personalized treatments, always bearing in mind that not all patients and not all P binders are equal.

**Keywords:** arterial stiffness, CKD, CKD-MBD, FGF23, KDIGO, phosphate, phosphate binder, prospective, pulse wave velocity, sevelamer

Chronic kidney disease (CKD) in general and the associated mineral and bone disorders (MBDs) in particular have both been related to markedly increased morbidity and mortality [1, 2]. In the context of CKD-MBD, phosphate (P) and fibroblast growth factor 23 (FGF23) are considered independent cardiovascular risk factors [3, 4]. In fact, P and FGF23 have been closely associated with left ventricular hypertrophy, vascular calcification (VC) and mortality, among other deleterious effects [5–7]. Many

studies, most of them performed in ‘dialysis’ patients, have clearly shown that P levels (high and low) and P binder treatment [8–10], high FGF23 concentrations (in both dialysis and CKD patients) [3, 4] and longitudinally increasing FGF23 trajectories [11] are associated with CKD progression, cardiovascular morbidity and/or mortality. Moreover, a number of experimental and observational studies, meta-analyses and randomized clinical trials (RCTs) have shown that calcium (Ca)-free-P

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binders (mainly sevelamer in dialysis patients) attenuate the progression of VC as compared with Ca-based P binders [12–15]. Ca-free P binders may also decrease the number of hospitalizations and improve survival, at least in some studies and subgroups of dialysis patients (i.e. those  $\geq 65$  years of age) [15–21]. However, these seemingly very positive results are still a matter of debate and controversy [18, 21], at least partly due to their important financial implications. Thus it is still considered not definitely proven that P-lowering treatment (by means of different P binders) clearly improves hard outcomes [18, 21]. In any case, lowering elevated P levels towards the normal range was suggested by the recent 2017 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for patients with CKD Stages 3a–5d [Guideline 4.1.2; evidence 2C] [22]. These guidelines also stated that decisions about P-lowering treatment (diet, dialysis and P binders) should be based on progressively or persistently elevated serum P (Guideline 4.1.5; not graded). In addition, it was suggested that the dose of Ca-based P binders should be restricted in adult patients (Guideline 4.1.6; the evidence grade was upgraded to 2B) [22, 23].

In contrast, new pathophysiological insights into P homeostasis and the roles of FGF23 and Klotho in early CKD have led to the performance of clinical studies to investigate the value of P-lowering therapies in CKD patients in whom hyperphosphataemia has not yet clearly developed [13, 24, 25]. Several reports have shown that not only dietary P restriction but also sevelamer and, in general, Ca-free P binders may decrease FGF23 levels [13, 26–28]. However, it is unknown whether lowering FGF23 improves hard outcomes and therefore whether targeting FGF23 could be a useful strategy. Consequently, the 2017 KDIGO guidelines emphasize the perception that early ‘preventive’ P-lowering treatment (i.e. in patients with early P retention represented by increased intact or C-terminal FGF23 levels without hyperphosphataemia) is currently not supported by data [22]. Although it is recognized that preventing, rather than treating, hyperphosphataemia may be of value in patients with CKD Stages 3a–5d, it is acknowledged that current data are inadequate to support either the safety or the efficacy of such a ‘preventive’ approach, encouraging research in this specific area [22].

Two important RCTs addressing hard endpoints were evaluated by the 2017 KDIGO review team in non-dialysis CKD patients, leading to the suggestions mentioned above. Di Iorio *et al.* [13], in a multicentre non-blinded pilot study, randomized 212 consecutive outpatients (CKD Stages 3–4) to receive either sevelamer or Ca carbonate without a placebo control. The P concentration was maintained at between 2.7 and 4.6 mg/dL (normal values) for patients with CKD Stages 3–4 and between 3.5 and 5.5 mg/dL for those patients reaching CKD Stage 5. In addition to the coronary artery calcification (CAC) score, assessed at study entry for up to 24 months, all-cause mortality and dialysis inception were recorded for up to 36 months. FGF23 was not measured. The authors found that sevelamer provided benefits with respect to all-cause mortality and in the composite endpoint of death and dialysis inception, but not dialysis inception alone. It could not be definitely proven whether these findings demonstrate that compared with Ca-based agents, Ca-free P binders offer either a potential for benefit or an absence of harm. In this context, it should be pointed out that many experimental and clinical studies have shown a vast array of pleiotropic effects of sevelamer beyond P and/or FGF23 control [28–30]. Most of these actions could theoretically have contributed to the positive impacts on VC and survival attributed to sevelamer

not only in dialysis but also in non-dialysis patients [13, 14, 16, 19].

In the second RCT evaluated by the 2017 KDIGO review team, Block *et al.* [25] analysed 148 non-dialysis CKD patients (Stages 3b–4) with normal or near-normal P levels [mean baseline serum P concentration 4.2 mg/dL (1.36 mmol/L)]. Patients were randomly assigned to receive one of three different P binders (sevelamer carbonate, lanthanum carbonate or Ca acetate) or matching placebo. While there was a small decrease in serum P concentrations in those allocated to active P binder treatment and a 22% decrease in urinary P excretion, no significant difference was observed in the change in C-terminal FGF23 levels between patients who received P binders versus placebo. Moreover, in contrast to the authors’ expectations, progression of CAC and aortic VC was found in the ‘active’ treatment group, whereas there was no progression in the placebo arm. Subgroup analysis suggested that this negative unexpected effect was accounted for by Ca acetate treatment. This explanation was further supported by a metabolic study [31] in a small group of eight patients with CKD Stages 3–4 in whom the addition of 1500 mg/day of Ca carbonate (3 weeks) caused a significantly positive Ca balance, as measured by Ca kinetics, without affecting baseline neutral P balance and with only a modest reduction in urine P excretion. This kinetic study demonstrated a positive net bone balance that was lower than the overall Ca balance, thus suggesting soft tissue deposition. This study also supported results reported previously by Spiegel and Brady [32] in six normophosphataemic adults with CKD Stages 3b–4 versus six normal control subjects in which potential harms of liberal Ca exposure in such cohorts was suggested (with total intakes as low as 800 and  $\sim 1000$  mg/day, respectively). However, due to the small number of patients and short duration, these studies were not considered to fulfil the predefined inclusion criteria for 2017 KDIGO full evidence review [22]. Moreover, the evidence grade was not higher because none of the studies provided sufficient dose threshold information about Ca exposure or information on the safety of moderately dosed Ca-based P binders [22]. Importantly, the Block *et al.* study [25] did not show a superiority of Ca-free P binders versus placebo in terms of progression of the CAC surrogate endpoint, calling into question the efficacy and safety of P binding in this particular population [22]. Nevertheless, it is worth considering that this study was exploratory and underpowered to detect differences between P binders.

In view of these considerations, the 2017 KDIGO guidelines state that in addition to the need to conduct Ca and P balance studies across all CKD stages, prospective RCTs should be undertaken to investigate the value of FGF23 levels (and possibly Klotho) as an indicator for establishing P-lowering therapies [22]. This is obviously especially relevant for non-dialysis CKD patients. More importantly, RCTs regarding patient-centred outcomes, major adverse cardiovascular events and/or survival endpoints seem urgently needed. In addition, the guidelines mention that the analysis of other endpoints such as CKD progression or cardiovascular calcifications would be desirable [22], although the latter is viewed as a hard but surrogate endpoint.

Following from this line of promising studies, in this issue of *Clinical Kidney Journal*, de Krijger *et al.* [33] report on an interesting evaluation of whether sevelamer carbonate induces an improvement in carotid femoral PWV (as the primary outcome) and whether this effect is mediated by a decline in FGF23. It is well known that PWV is a measure of arterial stiffness and a

surrogate marker for cardiovascular calcification, cardiovascular events and all-cause mortality, including in patients with CKD [34].

Sevelamer was the first polymer developed as a P binder for patients with CKD, and there is now >20 years of clinical experience in its use within the context of a multiple therapeutic approach to CKD-MBD (including vitamin D, calcimimetics and/or Ca supplements) [35, 36]. Sevelamer carbonate (instead of hydrochloride) was subsequently developed mainly because patients with CKD are already predisposed to developing metabolic acidosis. Sevelamer carbonate received approval for use not only in dialysis patients but also in adult non-dialysis CKD patients with P levels  $\geq 1.78$  mmol/L (5.5 mg/dL). It has also been recently approved for the control of hyperphosphataemia in paediatric patients ( $\geq 6$  years of age and with a body surface area  $\geq 0.75$  m<sup>2</sup>) [37].

The above-mentioned study by de Krijger *et al.* [33] is a prospective, single-centre, single-arm pilot analysis in 24 normophosphataemic CKD Stage 3 patients [mean estimated glomerular filtration rate (eGFR)  $43 \pm 10$  mL/min/1.73 m<sup>2</sup>]. The authors found that treatment with a high fixed dose (2.4 g twice daily) of sevelamer carbonate over 8 weeks did not induce a significant reduction in PWV [ $9.2 \pm 2.3$  versus  $8.7 \pm 2.4$  m/s ( $P = 0.12$ ); PWV values  $< 8$  m/s were defined as normal] in the 18 patients who completed the study. Moreover, FGF23 did not decrease during treatment, although a decline in 24-h urinary P excretion was observed. Also, serum P concentration did not change during this period (after excluding, per protocol, three patients who developed hypophosphataemia after 1 week of treatment). Therefore, to some extent, these results do not support the assumption of beneficial effects of early treatment of P exposure to improve cardiovascular risks in all CKD patients, at least as evaluated by PWV.

Nevertheless, it is very interesting that the authors report that in a subgroup of patients with absent or limited abdominal VC (lower Kauppila score), treatment resulted in a statistically significant reduction in PWV after the necessary adjustment for mean arterial pressure. This potential benefit in terms of PWV improvement in a subset of patients could not be reliably attributed to a change in FGF23, rather it seemed more likely to have been induced by lower P exposure (represented by a lower urinary excretion of P). The effect of sevelamer on PWV appeared to be independent of FGF23 after elegant statistical analysis. Thus the subgroup results suggest that PWV is at least amenable to improvement by 'preventive' treatment over this short period of time, at least in CKD patients with a low calcification score. Short-term modifications of PWV and of the augmentation index (as a measure of arterial wave reflections) have been described with L-arginine or statins in several non-CKD studies within 2–3 days or 8 weeks, respectively [38, 39]. In CKD (Stages 2–4) patients, L-arginine resulted in a significant improvement of both carotid–femoral PWV ( $13.06 \pm 2.65$  versus  $10.62 \pm 1.93$  m/s) and augmentation index after 12 weeks of follow-up [40].

It is known that PWV may be greatly increased even in the early stages of CKD [34]. Many possible reasons have been put forward to explain progressive stiffness as eGFR declines, including endothelial dysfunction, subclinical atherosclerosis, VC and CKD-MBD-related factors, among many others [34]. All these factors may already be present in non-dialysis CKD and they have also been associated with P and/or FGF23 through mechanisms not completely elucidated. In fact, severe VC (a factor that contributes to arterial stiffness but is unlikely to be modifiable with such a short-term intervention) is already frequently present in non-dialysis CKD, as described by us and

many others [41, 42]. Of utmost interest is the recognition by de Krijger *et al.* [33] that the degree of VC will have to be taken into account when analysing these potential quick vascular responses to treatments. In incident peritoneal dialysis patients, it was previously shown that PWV can change in either direction at >6 months and that changes are associated with modifiable risk factors such as the use of Ca-based P binders [43]. In hyperphosphataemic haemodialysis patients, other authors have reported that treatment with sevelamer attenuated within 6 months the progressive increase in PWV observed during Ca carbonate treatment [44]. Sevelamer >11 months was also associated with an improvement in aortic stiffness without affecting the serum levels of several inhibitors of VC [45]. Neither measurements of FGF23 nor VC were evaluated in these studies.

In a different CKD setting, no effect of sevelamer on PWV or on intact FGF23 was found in a 10-month study in which 109 normophosphataemic patients with CKD Stage 3 were randomized to sevelamer or placebo [46], perhaps because PWV results were not corrected for blood pressure (a PWV key determinant). While a subgroup analysis of highly compliant subjects revealed significant decreases in FGF23 and urinary P concentration in patients receiving sevelamer (versus placebo), no difference in serum P or Klotho was observed.

Interpretation of all these scarce and heterogeneous observations remains difficult. Different CKD stages, lack of standardization of P and Ca intake, different doses and type of P binders and/or vitamin D compounds, the presence of controls, measurement of different FGF23 molecules, different basal laboratory or PWV values, unidentical adjustments of PWV parameters or arterial pressure control, diverse case mixes and differences in statistical power analysis may all have contributed to the observed wide scattering of results. It is also important to note that the reported decline in eGFR may also justify the lack of beneficial effect of sevelamer on FGF23 levels, blurring potential expected effects of treatment. FGF23 did not decrease despite potentially declining calcitriol levels (due to renal function impairment and/or sevelamer interference with absorption of liposoluble vitamins). In fact, after correcting for eGFR/calcitriol, a statistically significant decline in FGF23 concentration was found following treatment [33]. More importantly, the authors [33] noted that the degree of VC has to be taken into account when trying to investigate early vascular changes or responses to treatments in this population. In other words, future studies aimed at improving cardiovascular risk by modifying early surrogate markers such as PWV should probably be focused on patients with limited VC. In contrast, although FGF23 (secondary outcome and linked to both P and Ca homeostasis) is reported to be closely associated with microvascular function in CKD [47, 48], in this real-life and other studies, changes in FGF23 did not seem directly related to PWV [33, 46]. However, causality and/or the possibility of preventive treatment of deleterious hyperphosphataemia in CKD patients may not yet be completely ruled out, since low discriminatory power may hinder the potential impact of any manoeuvre or mechanistic pathway analysis.

In summary, de Krijger *et al.* [33] provide nice original information that contributes to an area in which nephrologists are in need of new information, clearer identification of sources of bias and identification of methodological issues that may lead to more personalized treatments, always bearing in mind that not all patients and not all P binders are equal [49]. In the meantime, we await clear-cut prospective RCTs in normophosphataemic patients that analyse really hard outcomes. This

is definitely one of the major gaps in knowledge that we currently face in the management of early CKD-MBD [49]. However, as recently shown in the CKD Optimal Management With BInders and NicotinamidE trial, reducing P and FGF23 in non-dialysis CKD may require completely new approaches [50] and, as stated in the current guidelines [22], potential P loading with normophosphataemia may not be an indication to start P binders. Whether disproportional elevations in serum FGF23 concentrations may become a signal to start P-lowering therapies or a future target with other drugs in early CKD will also need to be investigated.

## CONFLICT OF INTEREST STATEMENT

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